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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,593	12/05/2001	Katherine S. Bowdish	1087-2	3532

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EXAMINER
HELMS, LARRY RONALD

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/20/2003

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/006,593	BOWDISH ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-95* is/are pending in the application.

4a) Of the above claim(s) *17,18,20,21,24-35,37-43,46-84 and 91-95* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,19,22,23,36,44,45 and 85-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-23, 36, 44-45, 83, 85-92, in Paper No. 11 is acknowledged. The traversal is on the ground(s) that both Groups I and V be examined concurrently because Group I and V relate to immunoglobulins that contain an EPO or TPO mimetic either by replacement of a CDR or fusion to a CDR and claims in Group II be examined with Group I. This is not persuasive. The nucleic acids in Group II are patentably distinct from those of Groups I or V as stated in the restriction requirement. In addition, the products of Groups I and V are distinct as stated in the restriction requirement because they are structurally distinct in that Group I requires replacement of a CDR and Group V requires fusion to a CDR which are structurally different. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is made **FINAL**.

2. It is noted that in the response to the restriction requirement that an election of SEQ ID NO:2 was elected. The response stated that claims 1-16, 18, 22-23, 36, 83, 85, 88, 89, 90 are believed to be generic and claims 19, 20, 21, 44, 45, 86, 87, 91, and 92 are believed to recite SEQ ID NO:2 (see page 2 of response). In response to this claim 18 recites the species of SEQ ID NO:1, claims 20-21 do not recite SEQ ID NO:2 and are not generic they recite other species. Claims 91 and 92 also do not recite SEQ ID NO:2 and are directed to other species. Therefore, claims 1-16, 19, 22-23, 36, 44-45, 85-90 are the claims that are generic and read on the elected species of SEQ ID NO:2 and are under examination.

3. Claims 17-18, 20-21, 24-35, 37-43, 46-84, 91-65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions. Applicant timely traversed the restriction (election) requirement in Paper No. 11.

Specification

4. The disclosure is objected to because of the following informalities:

The application listed on page 55, line 3 is now a US Patent and should have the patent number recited in the specification.

Appropriate correction is required.

Information Disclosure Statement

5. The Information Disclosure Statement filed 7/19/02 has been considured in part. All US Patents listed on the IDS have been considured, however, all other references were not considured because copies of the references were not in the file. The examiner apologizes for any inconvenience but requests that copies of the references be supplied and the references will be considured at that time.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-16, 19, 22-23, 36, 44-45, 85-90 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-16, 19, 22-23, 36, 44-45, 85-90 are indefinite for reciting abbreviations "EPO" and "TPO" in claim 1. Full terminology should be in first instance of the claims followed by the abbreviation in parentheses. Dependent claims may then use the abbreviation. Abbreviations render the claim indefinite because the same abbreviation may represent more than one element or concept.

b. Claims 4, 12, 14-16, 45, 90 are indefinite for because it is not if more that one CDR is to be replaced with the same sequence or another sequence.

c. Claim 85-89 are indefinite for reciting "biologically active peptide is flanked at both its carboxyl terminus and its amino terminus" in claim 85 because claim 85 depends on claim 44 which requires a proline at the C terminus and the claims are indefinite because it is unclear if the claims require a proline at both ends of the peptide.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-16, 19, 22-23, 36, 44-45, 85-90 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunoglobulin

molecule or fragment thereof wherein one or more CDRs are replaced with a TPO mimetic wherein the immunoglobulin molecule or fragment binds thrombopoietin receptor, does not reasonably provide enablement for an immunoglobulin molecule or fragment that comprises replacement of a CDR with a TPO mimetic and the molecule does not bind the thrombopoitin receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to an immunoglobulin or fragment that comprises replacement of at least a portion of one CDR with a TPO mimetic and the molecule does not bind the receptor. The specification teaches replacement of CDRs with TPO sequences wherein the sequences are the same in the CDRs and the molecule binds the receptor (see Example3). The specification does not enable a molecule that does not bind the receptor.

As evidenced from Dower et al (US Patent 5,869451, issued 2/99) peptides for the TPO receptor are screened and bind to the receptor by using a screening method

(see column 17-18) and these compounds can be used to treat patients. As such one skill in the art would not know how to use an immunoglobulin or fragment thereof that did not bind to the receptor.

Therefore, in view of the lack of guidance in the specification and in view of the discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-16, 19, 22-23, 36, 44-45, 85-90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas et al [a] (WO 94/18221, published 8/94) and further in view of Dower et al (WO 96/40750, published 12/96) and Barbas et al [b] (PNAS 92:2529-2533, 1995) and as evidenced by Helms et al (Protein Science 4:2073-2081, 1995).

The claims are summarized as an immunoglobulin or fragment thereof wherein the immunoglobulin or fragment is anti-tetanus toxoid and a human antibody and comprising wherein the residues corresponding to at least a portion of at least one or two CDRs are replaced with SEQ ID NO:2 wherein the fragment is a Fab or full IgG from and the CDR is on a light chain and/or a heavy chain and the CDR is CDR3 and/or CDR1 or CDR2, and the peptide is flanked by a proline at the C terminus and has an amino acid at its N terminus and the flanking sequence is from several two amino acid peptides (claims 86-89) and compositions comprising such.

Barbas et al teach replacing CDRs in a heavy or light chain of an antibody or Fab fragment with biologically active peptides and randomizing the flanking sequences for presenting a biological active peptide in a conformation for binding to a receptor for example (see page 5, 8, 17, lines 5-33, page 19-20, page 26-27, 28-29, 53, 144, 149).

Barbas et al does not teach replacing a CDR with an TPO mimetic of SEQ ID NO:2 or the scaffold is the anti-tetanus toxoid antibody. These deficiencies are made up for in the teachings of Dower et al and Barbas et al [b].

Dower et al teach peptide sequences of TPO that bind the thrombopoietin receptor and SEQ ID NO:2 without the proline at the C-terminus (see page 26-30 and Table 7 and 9) and the addition of flanking sequences for structural constraints (see page 9).

Barbas et al [b] teach replacement of CDR3 in the anti-tetanus toxoid antibody with several sequences.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the anti-tetanus antibody as a scaffold to present SEQ ID NO:2 in one or two CDRs of the heavy or light chain of the antibody.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the anti-tetanus antibody as a scaffold to present SEQ ID NO:2 in one or two CDRs of the heavy or light chain of the antibody because Barbas et al [a] teach antibodies with several peptide sequences replacing the CDRs in an antibody and the molecules bind the target receptor and suggest that other sequences for other receptors would also work in replacing the CDRs. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the anti-tetanus antibody as a scaffold to present SEQ ID NO:2 in one or two CDRs of the heavy or light chain of the antibody because

Barbas et al [b] teach replacement in the anti-tetanus antibody of unrelated sequences from that in the CDR and the antibody binds the target and since antibody tertiary structures are homologous one skill in the art would conclude that the anti-tetanus antibody could be used for other sequences to present. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the anti-tetanus antibody as a scaffold to present SEQ ID NO:2 in one or two CDRs of the heavy or light chain of the antibody because Dower et al teach peptides that are fusion proteins and the peptides need to be constrained to be active (see page 42, line 10). It would have been obvious to use an antibody as a scaffold to present the TPO peptide because in solution peptides can be a random configuration and the scaffold constrains the peptide and presents it in a conformation that is better for binding and it would have been obvious to have residues flanking the sequence for presentation and it would have been obvious to use a proline at the C-terminus because as evidenced by Helms et al it is know in the art that proline residues decrease the conformational flexibility of a peptide (see page 2078) and thus would constrain the peptide.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

14. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

LARRY R. HELMS, PH.D
PRIMARY EXAMINER